Treatment with digoxin and measurement of serum digoxin levels after myocardial infarction

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Forty-nine patients admitted to a Coronary Care Unit with myocardial infarction complicated by left ventricular failure, were treated with 1.75 mg Lanoxin over 36 hours. Serum digoxin levels were measured by radioimmunoassay at 8, 24, and 48 hours. No difference in serum levels was observed between those patients who received 'old' (reduced bioavailability) and those who received 'new' Lanoxin. Serum levels were significantly higher at 8 and 24 hours in those patients who received their first dose intramuscularly compared with those who received their first dose orally, irrespective of the bioavailability of the oral preparation used. No correlation was observed between serum digoxin levels and serum urea or creatinine during the 48-hour period of study. The incidence of arrhythmias is reported, but no conclusion can be drawn as to whether or not the glycoside contributed to this in any way. The use of digoxin in patients with acute myocardial infarction complicated by left ventricular failure is justifiable in the light of available evidence. However, in view of the possible predisposition of such patients to toxicity, lower serum levels than were achieved in many of our patients seem desirable, and a modified dosage schedule is suggested.

Controversy concerning the indications for, and effectiveness of, digitalis therapy in patients with acute myocardial infarction still exists, as does concern about enhanced toxicity in such patients. Early investigations (Bing *et al.*, 1950; Blain *et al.*, 1956; Sarnoff *et al.*, 1964) suggested that digitalis had no effect on, or else reduced, myocardial oxygen consumption (MVO₂), which was inconsistent with the observations that the drug augmented the velocity of fibre shortening, which is an important factor in determining MVO₂ (Sonnenblick *et al.*, 1965). More recent work has demonstrated that while digitalis significantly increases MVO₂ in the non-failing canine heart, it has no effect on, and in some cases reduces MVO₂ in the failing heart (Covell *et al.*, 1966). This is presumably caused by a reduction in end-diastolic volume and hence systolic tension which offsets the increase in MVO₂ caused by increased contractility.

Early experimental evidence indicated that digitalis facilitated ectopic activity in the presence of infarction (Bellet, Johnston, and Schechter, 1934; Travell, Gold, and Modell, 1938), and more recent

evidence has suggested that the intoxicating dose is reduced by about one-third after acute myocardial infarction (Morris *et al.*, 1969).

While routine use of digitalis in uncomplicated myocardial infarction is contraindicated, its use early in the treatment of heart failure and cardiomegaly complicating acute myocardial infarction seems justifiable in the light of available evidence (Ratshin *et al.*, 1971; Karliner and Braunwald, 1972). This study was planned in order to gain some idea of the serum digoxin levels obtained in patients who were given digoxin after acute myocardial infarction complicated by left ventricular failure.

Patients and methods

Forty-nine patients were admitted to a coronary care unit between November 1971 and March 1973 with myocardial infarction and left ventricular failure. The presence of myocardial infarction was diagnosed on the basis of characteristic clinical presentation, electrocardiographic and serum enzyme changes. Left ventricular failure was manifested by dyspnoea, gallop rhythm, pulmonary venous congestion, and usually interstitial oedema, or frank pulmonary oedema. Digoxin was administered according to a routine protocol using Lanoxin tablets and intramuscular preparation (Burroughs Wellcome & Co.). The total dose was 1.75 mg, given in divided doses of 0.75 mg, 0.5 mg, 0.25 mg, and

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0.25 mg at 0, 8, 16, and 36 hours, respectively. The time between the onset of infarction and the first dose of digoxin varied from 6 hours to 7 days, the interval for most cases being between 24 and 48 hours. The first dose was given either intramuscularly or orally in a random order. After the 48-hour study period further dosage of digoxin was judged on an individual basis and in some cases the drug was discontinued. No patient subsequently received more than 0.25 mg daily. All patients were receiving oral frusemide 40 to 80 mg daily which was started either at the start of digoxin administration or up to 24 hours previously. Oral potassium supplements (48 mmol daily) were given routinely as Slow K tablets (Ciba).

Serum digoxin, urea, creatinine, and potassium levels were measured immediately before the first dose of Lanoxin, and 8, 24, and 48 hours later. All serum digoxin estimations were made at least 8 hours after the previous dose of Lanoxin. The serum digoxin was measured in duplicate by radio-immunoassay (Smith, Butler, and Haber, 1969), using antibody supplied from St. Bartholomew's Hospital, London. Serum urea, creatinine, and potassium were measured on an SMA 6-60 auto-analyser. A note was made of other treatment administered during the period of observation and the patients' electrocardiographs were monitored continuously for arrhythmias, an hourly rhythm strip being recorded in each case.

In May 1972, the process of manufacturing Lanoxin tablets was changed, so that a new oral preparation having twice the bioavailability of the old preparation was produced. In fact, this change restored the bioavailability of digoxin from Lanoxin tablets to the level which existed until 1969 (Johnson *et al.*, 1973). The Lanoxin tablets in our Hospital were changed for the new preparation in August 1972, and checks with the Hospital pharmacy and Burroughs Wellcome & Co. (N.Z.) Ltd. confirmed that all tablets supplied after this date were of the new bioavailability standard. We elected to continue our trial with the new preparation, though the change had not been anticipated at the start of the study. No change was made in the intramuscular preparation used throughout the period of study.

Twenty-six patients received the 'old' oral preparation, 14 having their first dose orally, and 12 their first dose intramuscularly. Twenty-three received the 'new' oral preparations, 11 having their first dose orally, and 12 their first dose intramuscularly. The serum digoxin levels were compared in all four groups, and correlated with serum urea and creatinine levels and cardiac arrhythmias.

Results

The serum digoxin level in all patients was zero at the start of the period of study and the levels in each group at 8, 24, and 48 hours are shown in Table 1 and the Fig. No significant differences in serum digoxin levels at 8, 24, and 48 hours between those receiving the 'old' and 'new' oral preparations were observed. When patients having their first dose of either preparation orally were compared with those having their first dose intramuscularly, however, levels were significantly higher in the latter group at 8 hours (2.5 nmol/l (1.95 ng/ml) compared with 1.35 nmol/l (1.05 ng/ml); $P < 0.001$), and 24 hours (3.01 nmol/l (2.35 ng/ml) compared with 1.79 nmol/l (1.5 ng/ml); $P < 0.005$). This difference was less pronounced and not significant at 48 hours (2.5 nmol/l compared with 2.0 nmol/l; $P > 0.1$ and less than 0.2). All groups were comparable with respect to age and serum urea and creatinine measured at the start of the period of study (Table 2). No significant correlation was found between the serum digoxin levels and the serum urea or creatinine, and no patient had a serum potassium level less than

FIG. Mean ($\pm$ SD) serum digoxin concentrations. Closed circles = 'Old' Lanoxin first dose I.M. Open circles = 'Old' Lanoxin first dose oral. Closed triangles = 'New' Lanoxin first dose I.M. Open triangles = 'New' Lanoxin first dose oral.

TABLE 1 Serum digoxin concentrations in nmol/l (figures are mean $\pm$ SD in each group)

Serum digoxin		8 hours	24 hours	48 hours
'Old' Lanoxin	First dose I.M.	2.43 $\pm$ 1.28	2.81 $\pm$ 1.10	2.56 $\pm$ 1.32
	First dose oral	1.40 $\pm$ 0.78	1.79 $\pm$ 0.91	2.05 $\pm$ 1.13
'New' Lanoxin	First dose I.M.	2.56 $\pm$ 1.19	3.07 $\pm$ 1.02	2.43 $\pm$ 1.04
	First dose oral	1.28 $\pm$ 0.36	2.04 $\pm$ 1.19	1.92 $\pm$ 0.93

Conversion SI Units to Traditional Units – digoxin 1 nmol/l $\approx$ 0.78 ng/ml.

TABLE 2 Serum urea and creatinine concentrations

		Mean age (yr)	Serum urea (mmol/l) Mean (SD)	Serum creatinine (μ mol/l) Mean (SD)
'Old' Lanoxin	First dose I.M.	62.7	8.5 (3.2)	132.6 (35.4)
	First dose oral	62.8	7.5 (3.2)	150.3 (44.2)
'New' Lanoxin	First dose I.M.	62.3	8.1 (2.5)	123.8 (26.5)
	First dose oral	57.4	7.3 (3.3)	123.8 (35.4)

Conversion SI Units to Traditional Units - 1 μ mol creatinine $\approx$ 0.011 mg; 1 mmol urea $\approx$ 6.0 mg/100 ml.

3.5 mmol/l (normal range 3.5-4.9 mmol/l) at any time during the 48-hour period of observation.

Thirteen patients were seen to have cardiac arrhythmias during the 48-hour period of observation as noted in Table 3. All three patients who had heart block had inferior infarcts. The patient who had asystole had an anteroseptal infarct with right bundle-branch block, a transvenous pacemaker having been inserted prophylactically before digoxin administration (Norris, Mercer, and Croxson, 1972). This patient was paced through the period of asystole but died 28 days later. Only one death occurred during the 48-hour period of digoxin treatment, from cardiogenic shock, but 13 patients died in hospital from 2 to 28 days after the initial standard digoxin administration was completed.

Discussion

The similarity of serum digoxin levels observed between our patients who received oral loading doses of the 'old' and 'new' Lanoxin preparations was surprising. The increased bioavailability of the new

Lanoxin preparation has been confirmed in several studies on patients receiving maintenance digoxin (Stewart and Simpson, 1972; Whiting, Rodger, and Sumner, 1972; Falch, Teien, and Bjerkelund, 1973), and in normal volunteers receiving loading doses (Falch *et al.*, 1973; Johnson *et al.*, 1973). However, our comparatively infrequent estimations of serum digoxin levels at 8, 24, and 48 hours after the initial dose may have provided an insufficient estimate of bioavailability. Better indices of bioavailability would have been provided by more frequent estimation of the serum digoxin level, and measurement of the area under the serum concentration/time curve and measurement of urinary digoxin excretion (Huffman and Azarnoff, 1972; Falch *et al.*, 1973; Sanchez *et al.*, 1973; Greenblatt *et al.*, 1973). The fact remains, however, that plasma levels were no different between the two preparations at the three times that they were measured.

The serum digoxin levels in those patients who received their first dose intramuscularly was higher than expected when compared with those who received their first dose orally, suggesting that the gastrointestinal absorption of the drug may be reduced in this group of patients. While it could be argued that this difference is caused by the delayed peak serum level reflecting a longer distribution and binding half-time of the drug when given by the intramuscular route, it is unlikely that any such difference would be present to such a significant degree at 8 and 24 hours after the initial intramuscular or oral dose. Single dose studies in healthy subjects have shown that the bioavailability of digoxin tablets is approximately half that of an equivalent dose given by the intramuscular route (Greenblatt *et al.*, 1973), and in patients with heart failure as a result of myocardial infarction, absorption of the oral preparation is likely to be further reduced and less predictable. While digoxin is incompletely absorbed when given by the intramuscular route (Doherty and Perkins, 1965), and bioavailability is less compared with intravenous infusion of an equivalent dose (Greenblatt *et al.*,

TABLE 3 Arrhythmias

		Serum digoxin (nmol/l) before develop- ment of arrhythmia
Paroxysmal atrial tachycardia	2	3.22, 3.46
Atrial fibrillation	3	0.64*, 2.18*, 2.30
Atrial flutter	1	2.30*
Second degree heart block	1	1.28
Complete heart block	2	1.28*, 1.79
Bigeminy	1	2.56
Ventricular tachycardia	2	1.02, 1.79
Asystole	1	4.61*
Total	13	

* Serum digoxin concentration at 8 hours.

Remainder - Serum digoxin concentration at 24 hours.

Conversion SI Units to Traditional Units - digoxin 1 nmol/l $\approx$ 0.78 ng/ml.

1973), the very high serum levels which are transiently produced after intravenous infusion would seem undesirable in this situation. Therefore, where rapid achievement of tissue-plasma equilibrium and optimal therapeutic levels is required as in this group of patients with heart failure caused by myocardial infarction, administration of the initial dose of digoxin intramuscularly seems preferable to oral or intravenous administration.

Accepting the evidence which suggests that patients with myocardial infarction are predisposed to digoxin toxicity (Morris *et al.*, 1969), one might have preferred to have seen serum digoxin levels slightly lower than were achieved in the majority of our patients who received their first dose intramuscularly; this suggests that a dose smaller than that used in our study is desirable. No conclusion can be drawn as to whether or not digoxin contributed to arrhythmias in our patients; the routine administration of potassium supplements and absence of hypokalaemia may be relevant in this respect. The lack of correlation between serum digoxin levels and serum urea and creatinine throughout the period of study further supports the recommendation of an empirical initial dose regimen in the acute situation. The concept of total body digoxin concentration relates to maintenance therapy only, and lean body mass is the only relevant factor to be considered in calculating a loading dose.

We suggest that the use of digitalis in left ventricular failure complicating myocardial infarction is reasonable, but its routine usage in the uncomplicated situation is not justifiable. We recommend that where digoxin treatment of such patients is contemplated, a total dose of no more than 1.5 mg (compared with 1.75 mg in this study) be administered during the first 36 hours, the first dose being 0.5 mg intramuscularly and the remainder being given in divided doses orally. Further dosage should be judged according to clinical response, body weight, and renal function, and wherever possible a 24-hour serum level should be measured to assist in this respect.

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